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PCBs, PCQs and PCDFs in Tissues of Yusho and Yu-Cheng Patients

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All five samples of oil involved in the recent Yu-Cheng outbreak were heavily contaminated with PCBs, PCQs and PCDFs at levels, on the average, of 62, 20 and 0.14 ppm, respectively. The samples not only had roughly one-tenth of the contamination by PCBs, PCQs and PCDFs but also three to four times lower ratios of PCQs and PCDFs to PCBs than samples of oil involved in Yusho in Japan. PCBs, PCQs and PCDFs present were all composed of similar congeners to the ones found in the Yusho specimens, though some variation of the component ratios of PCBs and PCDFs were observed.

On the other hand, five patients with Yusho who died 1 to 10 years following poisoning had markedly higher tissue levels of PCDFs and PCQs than did a worker occupationally exposed to PCBs. Taking great differences in the process of the healing and the tissue levels of PCBs, PCQs and PCDFs between the two poisoning cases into consideration, PCDFs and PCQs—especially the former—and not PCBs are deduced to be strongly associated with the development of Yusho.

Introduction

In 1968, Yusho occurred in the western part of Japan as a result of ingestion of a rice-bran cooking oil contaminated with a polycholorinated biphenyl (PCB) product. This occurrence affected about 1800 people and was clinically characterized by acnelike dermal lesions and a variety of constitutional symptoms (*1*). Many patients have been suffering from it for over 10 years, though the blood levels of PCBs declined rapidly once oil ingestion was terminated and 5 years later were only a few times larger than those of unexposed persons (*2*). On the other hand, in the cases of workers occupationally exposed to PCBs, only a minority had mild dermal lesions, despite high PCB levels in the blood. Discontinuation of handling PCBs resulted in the rapid disappearance of dermal symptoms in the occupationally exposed group (*3,4*). Thus, Yusho is clearly symptomatically different from the occupational PCB poisoning. In Japan, however, there has been a tendency to treat cases of the latter or the effect of PCBs as general environmental pollutants as being identical to Yusho.

In 1979, another Yusholike disease (Yu-Cheng) occurred in central Taiwan, the Republic of China, with a similar cause as in the case of Yusho (*5*). About 1700 persons have been suffering from obstinate symptoms as in the Japanese patients.

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The purpose of our study is to clarify etiologically the difference between both Yusho and Yu-Cheng on the one hand and simple PCB poisoning on the other.

Experimental and Materials

Five samples of rice-bran oil involved in the Yu-Cheng outbreak, which had been used in Hui-Ming School for Blindness and by the families of the poisoned patients in Taitung Country were collected in 1979. Their production dates were not known. They were kindly presented by Dr. T. C. Tung, Faculty of Medicine, National Taiwan University, and Dr. C. W. Huang, Department of Chemistry, Chung-Yuan University. Samples of the liver and adipose tissue or intestine of five Yusho patients taken at autopsy were obtained from Dr. I. Taki, Faculty of Medicine, Kyushu University. The tissues of normal individuals were obtained at autopsy after accidental death in September 1978. The milk of a female worker occupationally exposed to PCBs was collected for analysis in October 1977, 11 years after she discontinued handling PCBs.

Chemicals

p- and *m*-Quaterphenyls were purchased from Analabs Inc. (North Haven, CT, USA). *o*-Quaterphenyl was obtained from Wako Pure Chemical Co. Ltd. (Osaka, Japan). *o,m'*-, *o,p'*- and *m,p'*-Quaterphenyls were kindly donated by Dr. A. Mochiike, Hiroshima Prefectural

Institute of Health. A polychlorinated dibenzofuran (PCDF) mixture containing 46.3 to 56.8 wt-% chlorine was purchased from Wako Pure Chemical Co. Ltd. The 2,3,6,8-tetrachloro-, 2,3,7,8-tetrachloro-, 1,2,4,7,8-pentachloro-, and 2,3,4,7,8-pentachlorodibenzofurans were kindly presented by Dr. Masuda, Daiichi College Pharmaceutical Sciences. Florisil (60–100 mesh) was activated at 130°C overnight. Alumina (neutral, activation: I) was obtained from Merck Co. Ltd. (Darmstadt, West Germany), and its water content was adjusted to 0.8%. Solvents, reagents, and the polychlorinated quaterphenyl (PCQ) standard used here are described elsewhere (*6*).

Analytical Procedure

The sample was analyzed for PCBs, PCQs and PCDFs according to a modified method described previously (*6*). The method was essentially an alkaline saponification of the sample (5 g) in 50 mL of 1 *N* KOH alcoholic solution for 1 hr under refluxing followed by extraction with *n*-hexane and differential fractionation of PCBs, PCQs and PCDFs with solvents of *n*-hexane (60 mL), 4% diethyl ether in *n*-hexane (40 mL), and acetone (80 mL), respectively, on a Florisil column (6 g, 1 cm ID). The first fraction contained PCBs, the second PCQs and the third PCDFs. Quantification of PCBs followed the procedure reported previously (*6*). A half aliquot of the second eluate was analyzed qualitatively by GC-MS. The rest was perchlorinated with antimony pentachloride and qualitatively analyzed by ECD-GC according to our previous method (*6*). The PCDF fraction was further purified on an almina column and analyzed by ECD-GC and GC-MS.

Results and Discussion

Comparison of PCBs, PCQs and PCDFs in Yusho and Yu-Cheng Oils

Chen et al. (*7*) have already determined PCBs and PCDFs in five samples of Yu-Cheng oil collected from a factory and school cafeterias and families of the poisoned patients in Taichung Country. They, however, failed to give quantitative data on PCQs for lack of standard compounds, despite their confirming the presence of PCQs by GC-MS fragmentography. In this study, we performed qualitative analysis for all PCBs, PCQs and PCDFs in another specimen of Yu-Cheng oil and investigated qualitatively and quantitatively the chemicals in this oil and the oil involved in Yusho.

As shown in Table 1, all five samples of Yu-Cheng oil collected from Hui-Ming school and the victims' homes were heavily contaminated with PCBs, PCQs and PCDFs at average levels of 62, 20, 0.14 ppm, respectively. The contamination by PCBs and PCDFs was of the same order as that (on that average 80 and 0.29 ppm, repectively, for PCBs and PCDFs) reported by Chen et al. (*7*). In addition, the concentration ratio (2.4×10^{-3}) of PCDFs to PCBs was rather close to the value (3.6×10^{-3}) reported by Chen. In the Yusho incident, most of the patients were reported to be residents of Fukuoka and Nagasaki Prefectures and to have ingested

Table 1. Concentrations of PCBs, PCQs and PCDFs and their ratios in various materials.

Sample	PCBs, ppm	PCQs, ppm	PCDFs, ppm	PCQs/PCBs, g/g	PCDFs/PCBs, g/g
Yu-Cheng oil					
Y-1[a]	51	10	0.14	2.0×10^{-1}	2.7×10^{-3}
Y-2[b]	54	18	0.10	3.3×10^{-1}	1.9×10^{-3}
Y-3[b]	69	24	0.18	3.5×10^{-1}	2.6×10^{-3}
Y-4[a]	22	9	—[c]	4.1×10^{-1}	—
Y-5[b]	113	38	—[c]	3.4×10^{-1}	—
Average	62	20	0.14	3.3×10^{-1}	2.4×10^{-3}
Yusho oil[d]					
Feb. 5, 1968[e]	968	866	7.40	8.9×10^{-1}	7.6×10^{-3}
Feb. 9, 1968[e]	151	490	1.90	3.2	1.3×10^{-2}
Feb. 10, 1968[e]	155	536	2.25	3.5	1.4×10^{-2}
Average	430	630	3.85	1.5	9.0×10^{-3}
Kanechlor 400[d]	999,800	209	33	2.1×10^{-4}	3.3×10^{-5}
Used Kanechlor 400[d]					
U-1[f]	968,400	31,000	510	3.2×10^{-2}	5.2×10^{-4}
U-2[g]	999,000	690	277	6.9×10^{-4}	2.8×10^{-4}
U-3[h]	961,900	28,000	20	2.9×10^{-2}	2.1×10^{-5}
Average	979,800	19,00	269	2.0×10^{-2}	2.7×10^{-4}

[a,b]Samples collected from a school cafeteria and victims' home, respectively.
[c]No analysis.
[d]Data in our early study (*8*).
[e]Production date.
[f,g,h]Kanechlor 400 used as a heat exchanger liquid for 14 years at 180–270°C, for 3 years at 200–220°C, and under unknown condition, respectively.

Table 2. Component ratio (%) of PCBs in samples of Yu-Cheng and Yusho oils.

Sample	Number of chlorine					
	3	4	5	6	7	8
Yu-Cheng oil						
Y-1	2	33	36	19	10	0
Y-2	2	34	36	19	10	0
Y-3	1	31	39	19	10	0
Y-4	2	32	39	18	9	0
Y-5	2	32	39	18	9	0
Yusho causal oil						
Feb. 5, 1968	8	45	32	12	4	0
Feb. 9, 1968	6	39	32	15	8	0
Feb. 10, 1968	3	33	38	17	8	0
Feb. 15, 1958	8	34	34	16	8	0
Unused Kanechlor 400	22	59	18	0	0	0

bottled and canned products containing a rice-bran oil manufactured on February 5, 1968, until the middle of the same month by K-Company (*9*). Although the number of Yu-Cheng samples examined was limited, from our analytical data and those of Chen et al. (*7*), they were found to have only roughly one-tenth of the contamination by PCBs, PCQs and PCDFs found in the Japanese Yusho samples (Table 1).

Both the Yusho and Yu-Cheng oils were reported to be contaminated with PCB products which had been used as a heat exchange liquid in the deodorization process of the oil (*7,9*). In the case in Japan, Kanechlor 400 (Kanegafuchi Chemical Industry Co. Ltd., Japan; chlorine content: 48 wt-%) had been used as the medium. When Kanechlor 400 (KC-400) is heated, as in use as a heat exchanger, for a prolonged period at temperatures exceeding 200°C, both PCQs and PCDFs are generated thermochemically from PCBs, resulting in the elevated levels of PCQs and PCDFs compared to the original sample (*8*) (see Table 1). Yusho samples, however, further had concentration ratios of PCQs and PCDFs to PCBs higher than did the used PCB products (Table 1). Our early study (*10*) revealed that the phenomenon was produced during the deodorization process at a temperature of 230°C at a reduced pressure of 2–3 mm Hg because of a difference in the vapor pressure of PCBs, PCQs, PCDFs (PCBs > PCDFs >> PCQs). Yu-Cheng samples were also found to have higher concentration ratios (3.3×10^{-1} and 2.4×10^{-3}, respectively) of PCQs and PCDFs to PCBs than those (2.0×10^{-2} and 2.7×10^{-4}, respectively) of used Kanechlor 400s (Table 1). This might be attributed to the same cause as seen in the Yusho case.

As shown in Table 2, Yusho samples contained quite different compositions of PCBs from that of the original Kanechlor 400, showing the higher chlorinated biphenyl congeners than tetrachlorinated biphenyl to increase in relative quantity. This was also found to occur during the deodorization process due to a great difference in the evaporation rate of the various PCB congeners from the processed oil (*10*). The composition of PCBs varied depending on the production date (Table 2),

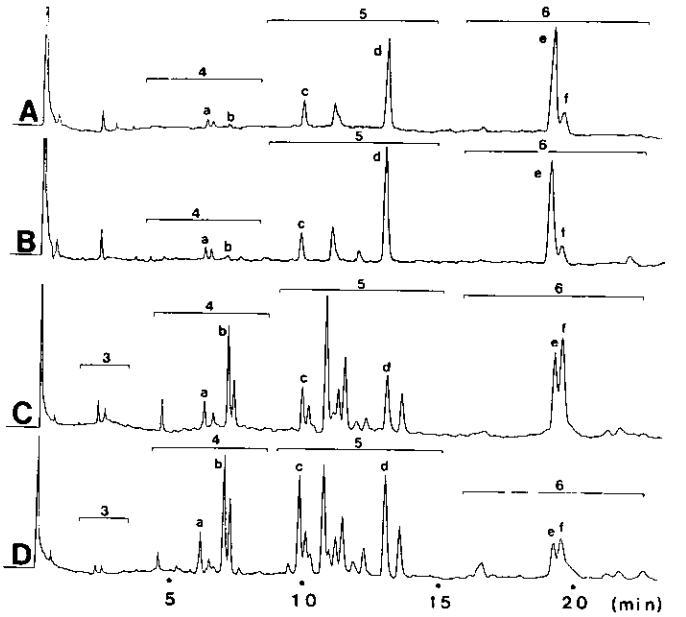

FIGURE 1. Capillary GC chromatograms, PCDFs in various materials: (*A,B*) PCDFs from the liver and adipose tissue, respectively, of a deceased patient with Yusho (case 1 in Table 3); (C,*D*) PCDFs from a sample of Yusho oil manufactured on February 5, 1968, and from a sample of Yu-Cheng oil, respectively. Numbers above the peaks designate the number of chlorine substituents as derived from GC–MS. Peaks a, b, c and d were identified as 2,3,6,8-tetrachloro-, 2,3,7,8-tetrachloro-, 1,2,4,7,8-pentachloro-, and 2,3,4,7,8-pentachlorinated dibenzofuran isomers, respectively; peaks e and f were deduced to be 1,2,3,4,7,8-hexachloro- and 1,2,3,6,7,8-hexachlorinated isomers, respectively, from the data of Rappe et al. (*16*). GC conditions: Varian Aerograph 2100 gas chromatograph equipped with ^{63}Ni-ECD; column, 25 m OV-17 capillary column; column, injector and detector temperatures 230, 240 and 300°C, respectively; carrier gas, N_2 (1 mL/min).

presumably due to a difference in the deodorizing conditions, especially deodorizing temperature. On the contrary, the Yu-Cheng specimens contained almost uniform compositions of PCBs in each of them (Table 2), indicating that the deodorizing conditions were constant thoughout the period when the PCB heat exchanger was leaking into the processed oil. PCBs present were composed of relatively larger quantities of higher chlorinated isomers than those in a Yusho oil of February 5, 1968, which was responsible for the majority of victims in Fukuoka Prefecture and rather similar to the oil produced on February 10, 1968 (Table 2).

As shown in Figure 1, both Yusho and Yu-Cheng specimens contained numerous isomers of trichlorinated to hexachlorinated dibenzofurans. A comparison between the gas chromatographic pattern of the PCDFs found in the two samples showed similarities although in some different proportions of several congeners. It is noteworthy that 2,3, 7,8-tetrachloro-, 2,3,4,7,8-pentachloro-, and 1,2,3,4,7,8-hexachlorinated dibenzofuran isomers were largely present in both purified sample extracts of both Yusho and Yu-Cheng oil, because they were all confirmed to be highly toxic (*11,12*).

Figure 2 shows GC–MS chromatograms showing the

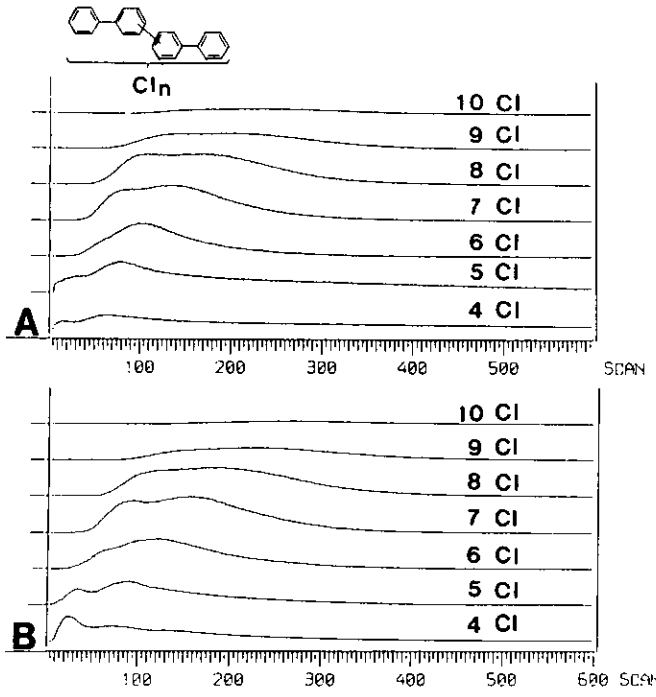

FIGURE 2. GC–MS chromatograms showing elution of PCQs in samples of Yusho and Yu-Cheng oils: (*A*,*B*) PCQs from a sample of Yusho oil manufactured on February 5, 1968, and from a sample of Yu-Cheng oil, respectively. GC–MS conditions: Hewlett Packard 5710A gas chromatograph-JEOL DX 300 mass spectrometer; column, 0.5 m × 2.2 mm glass column containing 2% OV-210 on Gaschrom Q (100/120); column injection, and ion source temps., 270, 270, and 290°C, respectively, electron energy, 70 eV; accelerator voltage, 3.0 kV; carrier gas, He_2 (30 mL/min).

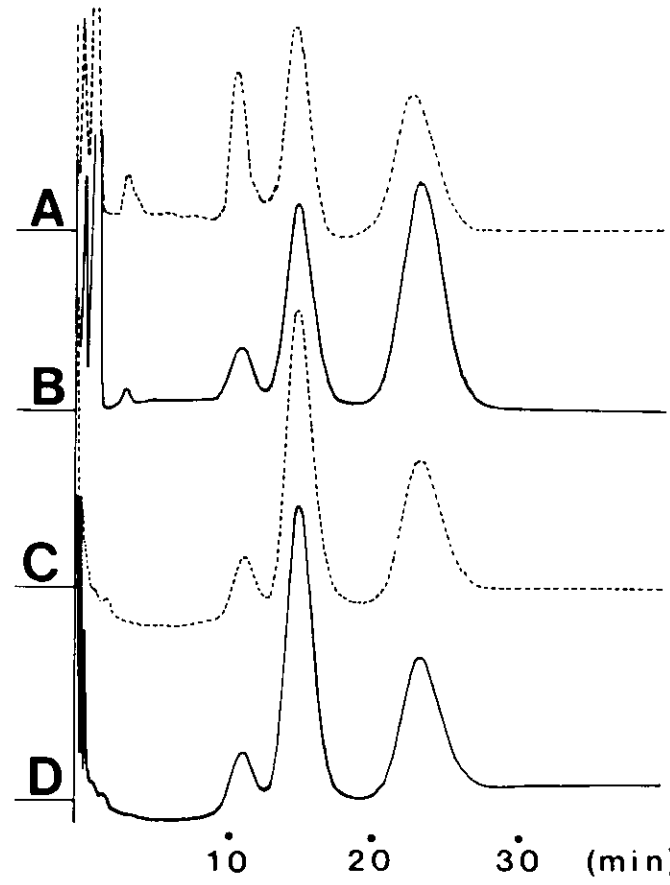

FIGURE 3. Gas chromatograms of PCQs in various materials after perchlorination: (*A*,*B*) perchlorinated PCQs from the adipose tissue and liver, respectively, of deceased patient with Yusho (case 1, Table 3) perchlorinated PCQs from a sample of Yusho oil produced on February 5, 1968, and from a sample of Yu-Cheng oil, respectively. GC condition: Shimadza GC-6A gas chromatograph eqipped with ^{63}Ni-ECD; column, 0.5 m × 2.6 mm glas column containing 2% SE-54 on Gaschrom Q (100/120); column injector and detector temperatures, 290, 300 and 300°C, respectively; carrier gas, N_2 (40 mL/min).

elutions of tetra- to decachlorinated quaterphenyl, respectively, in Yusho and Yu-Cheng oils. Each GC-MS chromatogram showed an unseparated broad peak, because of the failure to separate individual PCQ isomers on the GC column; in all there may exist more than hundreds of thousands of congeners. As shown in Figure 2, the oils involved in both incidents contained similar compositions of PCQs including hexachlorinated through octachlorinated congeners as the major components. In our study (*10*), no PCQ congeners were removed from the processed oil in the deodorization tank during the deodorization process. Therefore, the compositions of PCQs present in the two oils might be identical to those in the original PCB products used as heat exchanger liquid for the deodorization of the respective oils.

An aliquot of purified PCQ extract from both oils was perchlorinated with antimony pentachloride in order to convert the numerous PCQ congeners into six octadecachlorinated quaterphenyls ($C_{24}Cl_{18}$, molecular weight: 927). After perchlorination, three peaks showed up in gas chromatograms as illustrated in Figure 3. The first the second and the third peaks were identified as their retention time, ion clustering due to the chlorine isotope and the major fragmentation products ($M^+ - Cl$, $M^+ - 2Cl$, $M^+ - 4Cl$, etc.) compared to authentic standards for octadecachlorinated *o*-quaterphenyl, a complex of octadecachlorinated *o,m'*- and *o,p'* isomers and a complex of octadecachlorinated *m*-, *m,p'*- and *p*-isomers. A similar result was reported in PCQs from a sample of used Kanechlor 400 by Mochiike et al. (*14*), indicating the concentration ratios of octadecachlorinated *o*- isomer, *o,p'*-, + *o,m'*- isomer, *p*- isomer, *o,p'*- isomer, and *m*-isomer to be 9.2, 57.8, 0.6, 16.7, and 16.7%, respectively. As shown in Figure 3, gas chromatographic patterns of perchlorinated PCQs were strikingly similar for the Yusho and Yu-Cheng samples, suggesting PCQs from both samples to have similar ratios of the six types in their basic makeup.

Taking all the above results into consideration, PCBs, PCQs and PCDFs in the Yu-Cheng samples were composed of similar congeners to the respective ones found in the Yusho oils, though some variations of the component ratios of PCBs and PCDFs were observed.

Table 3. Concentrations of PCBs, PCDFs, and, PCQs in the tissues of Yusho patients, unexposed individuals and in the milk fat of a worker occupationally exposed to PCBs.

Case	Age	Sex	Time after exposure yr.	Tissue (or fluid)	Concentration, ppb PCBs[a]	PCDFs	PCQs[a]
Yusho patients							
1	25	M	1	Adipose tissue	5090	5.3	2400
				Liver	226	70.1	218
2	46	F	4	Adipose tissue	6091	9.6	1444
				Liver	68	15.5	144
3	72	M	7	Intestine	3472	2.5	1770
				Liver	114	6.2	51.7
4	59	M	9	Intestine	3630	2.2	416
				Liver	64	6.1	6.3
5	59	M	9	Intestine	1273	0.2	24.5
				Liver	18	0.02	0.97
Unexposed individuals							
Avg.	53	M,F	–	Adipose tissue	803[b]	0.019[b]	1.53[b]
				Liver	33[b]	0.006[b]	0.41[b]
PCB worker							
	37	F	11	Milk fat	6241	0.02	0.2

[a]Data in our early study (*15*).
[b]Average concentration from 14 persons.

Differences in the Amounts of Tissue PCBs, PCQs and PCDFs in Exposed and Unexposed Workers

The concentrations of PCBs in the tissues of patients with Yusho (cases 1 and 2) who died within a few years following poisoning were only several times those in unexposed individuals (Table 3). The tissue level gradually decreased with time following the intoxication, and in one patient (case 5) who died in 1979, the level was close to that of the control group. The levels of PCQs and PCDFs, as well as PCBs, in the tissues of deceased patients gradually declined subsequent to the incident (Table 3). The tissue levels of PCQs and PCDFs, as well as PCBs, however remained extremly elevated for 10 years compared to those of the control group. For example, even a patient (case 4) who died 9 years following poisoning, had a PCDF level 1016 times higher and PCQ level 15 times higher in his liver than did unexpsed individuals. On the other hand, in an exposed worker (Table 3) diagnosed as a case of an occupational PCB poisoning, the dermal lesions—chloracne and dark-colored pigmentation—disappeared quickly after discontinuation of handling PCBs. Even 11 years after the termination of exposure, however, the level of PCBs in her milk fat was fairly high, whereas the level of PCDFs or PCQs was similar or lower, respectively, compared to that in the adipose tissue of the control individuals. Therefore, the high contamination by PCQs and PCDFs is thought to be characteristic of Yusho patients.

A rapid reversal of clinical symptoms after termination of PCB exposure was reported as common in occupationally exposed workers whose daily intake (4–12 mg) (*3*) of PCBs was similar in quantity to that (7.9 mg) (*16*) ingested by Yusho patients, despite high blood levels of PCBs as much as 10 to 100 times that of the control (*3,4*).

From all the above facts, PCDFs and PCQs (other than PCBs) are deduced to be strongly associated with the development of Yusho.

When compared to original PCDFs ingested by the patients which contained 20 to 40 congeners, their number in the tissues was markedly decreased to about 10 (Fig. 1). The tissue PCDFs were composed of 2,3,4,7,8-pentachloro- and 1,2,3,4,7,8-hexachloro isomers as the major components and 2,3,6,8-tetrachloro-, 2,3,7,8-tetrachloro-, 1,2,4,7,8-pentachloro-, and 1,2,4,6,7,8-hexachloro- isomers as the minor components. A similar result was also reported in the adipose tissue and liver of a deceased patient with Yusho by Rappe et al. (*16*). Considering the extremely high toxicity (*11,12*) and strong hepatropism (Table 3) (*12,16,17*) of the two major constituents, they might be responsible agents for the lingering symptoms seen in the patients.

PCQs in the liver of deceased patients gave a much broader gas chromatographic peak including highly chlorinated quaterphenyl congeners, while in the adipose tissue there was a sharper peak composed of mainly lower chlorinated congeners. After perchlorination, there was also a difference in the gas chromatographic pattern of the two tissues, showing an increase of the third peak in the liver and first peak in the adipose tissue compared to that of the original PCQs (Fig. 3). In our experiment (*18*), both after and before perchlorination, the gas chromatographic pattern of PCQs retained in the treated monkeys' body varied from tissue to tissue, showing to be distinguishable from the case of PCBs.

From these results, the tissue distribution of PCQs is surmised to be closely related not only to the number of chlorine substitution but also to the nature of the carbocylic structure.

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